REMARKS

This Amendment is being submitted in response to the Office Action dated March 20, 2009 in the above-identified application. Applicants note that June 20, 2009 falls on a Saturday, therefore, the time for filing a response to the March 20, 2009 Office Action is thereby extended to Monday, June 22, 2009, and this Amendment is being timely filed. If it is determined that any additional fee is due in connection with this filing, the Commissioner is authorized to charge said fees to Deposit Account No. 50-0552.

Claims 1-31 were originally pending. Applicants previously canceled the original claims and presented the elected claims as new claims 32-37 and added claims 38-46. Accordingly, claims 32-46 were pending for purposes of the instant action. All claims stand rejected.

Claim 32 has been amended. Support for the amendment to claim 32 can be found in the present specification, for example, in paragraphs [0051], [0058] and Examples 3 to 12 of U.S. Publication No. 2006/0167092 of the present specification.

Claims 38, 39 and 46 were amended to correct an obvious typographical error. Specifically, claims 38, 39 and 46 depend from claim 32 which recites Formula (I), therefore claims 38, 39 and 42 have been amended to recite Formula (I), not Formula 1 as previously recited.

Applicants respectfully submit that no new matter has been added by the above amendments to the claims. Dependent claims 35 to 37 have been amended to provide proper antecedent basis to independent claim 32 as amended. Dependent claims 41 and 43 have been amended to provide proper antecedent basis to independent claim 32 as amended.

Reconsideration of these currently pending claims is respectfully requested.

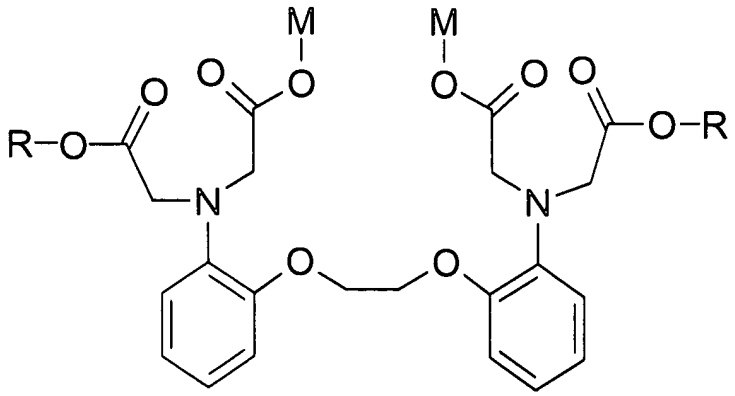
I. Claim Rejections under 35 U.S.C. § 112

Claims 32 to 46 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not providing "enablement for the treatment or management of a metalloproteinase-related disease or disorder selected from cancer recited in claim 32." See Office Action, page 2, third full paragraph.

The Office Action states, *inter alia*, that "the instant claims cover the treatment of diseases, such as autoimmune disease and cancer, for which there is no enablement provided." See Office Action , page 3, lines 12-13.

Claim 32 has been amended to recite: A method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of metalloproteinase (MMP) or calpain found in a normal mammal comprising administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I):

(I)



wherein

R is saturated or unsaturated alkyl, cycloalkyl, arylalkyl or cycloalkyl-alkyl radical having from 1 to 28 carbon atoms which may be interrupted by any combination of 1-6 oxygen and/or nitrogen atoms, provided that no two oxygen atoms or an oxygen and a nitrogen atom are directly connected to each other; and

M denotes a hydrogen or a physiologically acceptable cation.

As evident in paragraphs [0051], [0058] and Examples 3 to 12 of U.S. Publication 2006/0167092 of the present specification, the present specification clearly enables a method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of metalloproteinase (MMP) or calpain found in a normal mammal comprising administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I) as now recited in amended independent claim 32. Specifically, paragraph [0058] of U.S. Publication No. 2006/0167092 of the present specification recites:

> It has now been shown by the inventors of the present invention that DP-BAPTAs can attenuate or block both basal MMP-9 activity and TNF.alpha.- or PMA-induced activation of MMP-9. DP-BAPTAs can also inhibit calpain activity. Hence, DP-BAPTAs may be useful in reducing deleterious protease activities in pathological conditions due, for example, to ischemia and inflammatory responses. Accordingly, DP-BAPTA compounds may be useful in preventing, treating or managing diseases and pathological conditions associated with harmful activities of matrix metalloproteinases or calpains.

Moreover, one of skill in the art would know which disease or disorder is related to an elevated level of metalloproteinase (MMP) or calpain which are well-known in the prior art. Applicants also respectfully direct the Examiner's attention to paragraphs 0060 to 0066 of the present specification as a representative, but not exhaustive, list of diseases and disorders which are related to an elevated level of metalloproteinase (MMP) or calpain.

Applicants maintain that the fundamental finding of the present invention that MMP and calpain are inhibited by the BAPTA diesters, viewed in conjunction with the vast amount of established literature that demonstrate the linkage between MMP or calpain activity and certain diseases and disorders provides sufficient enablement for the treatment of diseases or disorders related to an elevated level of metalloproteinase (MMP) or calpain as recited in independent claim 32 in the present invention.

Moreover, the pre-clinical, in-vitro data presented in the subject application, e.g. Examples 3 to 12, clearly support the claims as currently recited, and would enable a person of ordinary skill in the art to practice the invention without undue experimentation. Specifically, as concluded in Example 4 of the present invention: "It was shown that the DP-BAPTA inhibitory effect on MMP-9 activity is in two levels: a) reduction of protein expression/release, and b) inhibition of MMP-9 enzymatic activity." See paragraph [0205] of U.S. Publication 2006/0167092 of the present specification. Therefore, the present specification enables: "A method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of metalloproteinase (MMP) or calpain found in a normal mammal comprising administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I)..." as recited in independent claim 32 of the present invention.

Applicants maintain that it is not necessary to conduct and present the results of clinical trials in order to claim a therapeutic activity as the Office Action appears to suggest. It is common knowledge in the art of drug development that a molecule that targets a key element which is essential for or contributes to the manifestation of a disease or disorder, is a potential candidate for serving as a medicament for treating such medical condition. Thus the finding of DP-BAPTA's inhibitory effect on MMP activity or calpain activity would enable one of ordinary skill in the art to use such compounds in "A method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of

metalloproteinase (MMP) or calpain found in a normal mammal..." as recited in independent claim 32 of the present invention.

Enablement for dependent claims 35, 41 and 42 may be found in paragraphs [0066] to [0070] and Examples 3 and 4, where DP-BAPTA compounds were tested, respectively, on rat and human glioma cell lines and were shown to reduce both basal and TNF-alpha-induced MMP-9 activities. It is well established that elevated expression of MMP-9 is associated with tumor proliferation and in particular with pathogenic mechanisms in cancer such as invasion, metastasis and angiogenesis. As recited in paragraph [0069] of the present invention:

> The inability to control metastasis presents a major problem, as metastases are the leading cause of death in patients with cancer. To date, there is no satisfactory treatment for preventing or limiting metastasis growth. Thus, the use of the DP-BAPTA compounds in accordance with the present invention for inhibiting MMPs, and in particular for inhibiting the MMP-9 protease activity, may be beneficial in this respect.

Therefore, MMPs, and in particular MMP-9, may be a rational target useful in the treatment of many types of cancer, including those types which are invasive, i.e., infiltrative (such as gliomas, as recited in paragraph [0066] of the present invention) or highly metastatic (as recited, for example, in paragraph [0069] and [0070] of the present invention) as recited in dependent claims 41 and 42 of the present invention.

Further enablement for dependent claim 36 may be found in Example 3, which shows that diesters of BAPTA inhibited both basal and TNF-alpha-induced MMP activity. As tumor necrosis factor alpha (TNF-alpha) is a pro-inflammatory cytokine and as MMP-9 is highly expressed at sites of inflammation and contributes to the pathogenesis of inflammatory diseases, applicants believe the recitation of a method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain, where the disease or disorder is an inflammatory condition or disease, as recited in dependent claim 36 of the present invention, is clearly supported by the present specification.

Example 8 demonstrates the effect of several DP-BAPTA molecules on the levels of TNF-alpha released in response to stimulation of primary glial cells with lipopolysaccharide (LPS). It was shown that the DP-BAPTA molecules were effective in reducing the induction of TNF-alpha release in primary glial cells. It is important to note that in this particular case the TNF-alpha release was induced by LPS, which is a bacterial component. In Example 9 it was also suggested that DP-BAPTAs may inhibit TNF-alpha release from macrophages.

In view of the above, applicants respectfully submit that, regardless of the cause of inflammation, any inflammatory disease or disorder associated with an elevated metalloproteinase (MMP) or calpain, which is mediated by the cytokine TNF-alpha and involves MMP-9 may benefit from treatment with diesters of BAPTA of the present invention.

The response refers primarily to independent claims 32 of the present invention, and the patentability of the dependent claims 33 to 46 follow at least for the reason of being dependent from independent claim that is patentable.

Reconsideration and withdrawal of the rejection under 35 USC 112, first paragraph, is respectfully requested.

II. Rejection of the Claims under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a)

Claims 32 to 39 and 44-46 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Kozak, et al. (WO 99/16741).

Independent claim 32 has been amended to recite: "A method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of metalloproteinase (MMP) or calpain found in a normal mammal comprising administering to a mammal in need thereof, a

pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I)..."

Kozak, et al. (WO 99/16741) discloses stable diesters of chelating agents of divalent metal ions, processes for their preparation and pharmaceutical compositions thereof, which are useful in a method for treating a condition or disease related to an excess of divalent metal ions, and in particular for the treatment of a condition or disease related to elevated levels of intracellular calcium ions. See abstract, Kozak, et al. (WO 99/16741).

35 U.S.C. § 102(b)

As stated in paragraph [0050] of the present invention:

> "[i]n the WO 99/16741 publication, the neuroprotective effects of DP-BAPTAs were demonstrated in neuronal cell cultures in-vitro, and in ischemia model systems in-vivo. However, the effect of the DP-BAPTA molecules on activities of specific enzymes has not been taught or suggested in that or any other publication. Accordingly, it was neither taught, recognized or suspected that these compounds could be effectively use for the treatment of MMP- and calpain-related diseases and disorders as disclosed in the present application."

Therefore, Kozak, et al. (WO 99/16741) discloses a method for treating a condition or disease related to an excess of divalent metal ions, and in particular for the treatment of a condition or disease related to elevated levels of intracellular calcium ions. Kozak does not teach or show "A method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of metalloproteinase (MMP) or calpain found in a normal mammal comprising administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I)..." as recited in claim 32 of the present invention. Because the cited reference does not describe each and every element of the current claims, the cited reference cannot anticipate the claimed invention.

The present Response refers primarily to independent claim 32 of the present invention, however, the patentability of the dependent claims 33-39 and 44-46 follow at least for the reason of being dependent from the independent claim that is patentable.

Reconsideration and withdrawal of the rejection under 35 102(b) is respectfully requested.

35 U.S.C. § 103(a)

Applicants note that the cited reference to Kozak (WO 99/16741) was discussed in the present specification at paragraphs [0025] and [0026]. Specifically, the present specification stated:

> [0025] Stable lipophilic diesters of the divalent metal ion chelator 1,2-bis(2 aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA) have been disclosed in the International Patent Publication No. WO 99/16741 of the same applicant. Also disclosed in this publication is the use of these compounds in pharmaceutical compositions useful for treating diseases and disorders related to excess of divalent metal ions. Among these diseases and disorders are ischemia, stroke, epilepsy and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.
>
> [0026] At that time, however, the mechanism by which these chelating agents exert their neuroprotective effects has not been elucidated or disclosed. No indication or suggestion for the cellular targets affected by these chelators has been mentioned in the WO 99/16741 or any other publication.

As stated in paragraph [0026] of the present specification, at the time of the present invention, "no indication or suggestion for the cellular targets affected by these chelators has been mentioned in the WO 99/16741 or any other publication." Therefore, WO 99/16741 did not teach or suggest "A method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of metalloproteinase (MMP) or calpain found in a normal

mammal comprising administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I)..." as recited in independent claim 32 of the present invention.

Moreover, as stated in paragraph [0050] and [0051] of the present specification:

> In the WO 99/16741 publication, the neuroprotective effects of DP-BAPTAs were demonstrated in neuronal cell cultures in-vitro, and in ischemia model systems in-vivo. However, the effect of the DP-BAPTA molecules on activities of specific enzymes has not been taught or suggested in that or any other publication. Accordingly, it was neither taught, recognized or suspected that these compounds could be effectively use for the treatment of MMP- and calpain-related diseases and disorders as disclosed in the present application.
>
> [0051] It is now disclosed, for the first time, that certain diesters of the chelating agent BAPTA are capable of inhibiting the activity of calpain and of certain proteases of the ADAM family, and in particular inhibiting the activity of matrix metalloproteinase-9 (MMP-9).

Therefore, at the time of the present invention, , it was neither taught, recognized or suspected by one of ordinary skill in the art that these compounds could be effectively use for the treatment of MMP- and calpain-related diseases and disorders as disclosed in the present application

In view of the foregoing, WO 99/16741 did not teach or suggest "A method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal as compared to the control level of metalloproteinase (MMP) or calpain found in a normal mammal comprising administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the Formula (I)..." as recited in independent claim 32 of the present invention.

Moreover, the cited Kozak reference (WO 99/16741) is directed to lipophilic diesters of chelating agents for the treatment of conditions and diseases related to elevated levels of divalent metal ions, and in particular, the treatment of conditions and diseases related to elevated levels of intracellular Ca^{++} ions. **By contrast, the subject application claims the use of these lipophilic diesters of the chelating agent (DP-BAPTAs) for treating conditions and diseases associated with elevated levels of metalloproteinase (MMP) or calpain activity**. Thus, the claimed invention concerns a method for treating or managing a disease associated with an elevated metalloproteinase (MMP) or calpain in a mammal via the inhibition of elevated levels of MMP or calpain activity by DP-BAPTAs. As stated in paragraph [0051] of the present specification, this aspect of the subject invention is disclosed for the very first time in the subject application and was not taught or suggested in the prior art – and particularly not taught or suggested by the Kozak reference (WO 99/16741).

In view of the foregoing, the claimed invention, as expressly recited, is unobvious in view of the Kozak disclosure.

This Response refers primarily to independent claim 32 of the present invention, however, the patentability of the dependent claims 33-39 and 44-46 follow at least for the reason of being dependent from independent claim that is patentable.

Reconsideration and withdrawal of the rejection under 35 USC 103(a) is respectfully requested.

III. CONCLUSION

A timely and favorable action in the subject application is respectfully urged.

Respectfully submitted,

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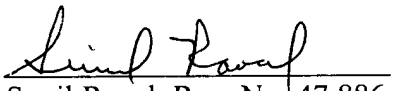
By: 
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